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Physiological Substrates of Mammalian Monogamy: The Prairie Vole Model

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CARTER, C. S., A. C. DEVRIES AND L. L. GETZ. *Physiological substrates of mammalian monogamy: The prairie vole model.* NEUROSCI BIOBEHAV REV 19(2) 303-314, 1995. —Prairie voles (*Microtus ochrogaster*) are described here as a model system in which it is possible to examine, within the context of natural history, the proximate processes regulating the social and reproductive behaviors that characterize a monogamous social system. Neuropeptides, including oxytocin and vasopressin, and the adrenal glucocorticoid, corticosterone, have been implicated in the neural regulation of partner preferences, and in the male, vasopressin has been implicated in the induction of selective aggression toward strangers. We hypothesize here that interactions among oxytocin, vasopressin and glucocorticoids could provide substrates for dynamic changes in social and agonistic behaviors, including those required in the development and expression of monogamy. Results from research with voles suggest that the behaviors characteristics of monogamy, including social attachments and biparental care, may be modified by hormones during development and may be regulated by different mechanisms in males and females.

Prairie voles Social behavior Attachment Monogamy Oxytocin Vasopressin Adrenal steroids
Corticosterone Sex differences

MONOGAMY IN MAMMALS

MONOGAMY has fascinated behavioral researchers for over a century. However, the concept of monogamy is complex and monogamy has been defined in sometimes contradictory terms (reviewed 33). Most definitions of monogamy, including those found in dictionaries (105), include reference to the importance of sexual or mating exclusivity. By such definitions monogamy is a mating system. Monogamy also has been defined as a social system. These definitions tend to emphasize the importance of long term associations or pair bonds between one male and one female, and the importance of biparental care. New methods for determining paternity have indicated that sexual exclusivity is comparatively rare. However, observations of mammalian species that have been described as either socially or sexually monogamous have revealed a cluster of unusual behavioral and reproductive features that taken together define monogamy (31,57). Among the traits that have been used to characterize monogamy are the following: (a) male and female cohabitation and long-term selective association or pair bonds throughout breeding and nonbreeding seasons; (b) selective aggression directed toward unfamiliar conspecifics; (c) biparental care, including high levels of paternal behavior, and alloparenting; (d) socially regulated reproductive processes such as estrus induction and ovulation; and (e) incest avoidance and reproductive suppression of adult indi-

viduals within a family group (that remain with the family as "helpers"). In the present paper we will use the term monogamy to refer to a social system in which animals exhibit all or most of the features described above.

Monogamy is uncommon in mammals, with an estimated occurrence of only three percent. The appearance of monogamous mating or social systems does not follow any obvious taxonomic or phylogenetic pattern. For example, tamarins, marmosets (1,86,90), titi monkeys (70), aardwolves (82), elephant shrews (81), California mice (49), prairie voles and pine voles (14,33) share many of the characteristics of monogamy.

Social organization and the ultimate or evolutionary causes for monogamy have been discussed by several sources (reviewed 6,65,72,106). It has been suggested that monogamous males increase their reproductive fitness by maintaining their association with a single female. In contrast, nonmonogamous males may abandon their mate to seek out additional sexual partners. Additionally, environments in which single parents are incapable of rearing the young may favor monogamy. In many species monogamy also involves paternal investment in the defense of or care of offspring from a single female partner (94).

In contrast, little is known regarding the proximate or physiological mechanisms underlying the expression of monogamy. In general, it has not been widely recognized that the characteristics of either a mating system or social system might

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have a physiological basis. However, the collective features of monogamy are reproductive and social behaviors which, in many species, have been shown to be modified by various hormones and neurochemicals. We propose here that endocrine factors from the adrenal and gonadal axes regulate the organization and expression of the social and reproductive patterns that characterize monogamy.

In the present paper, prairie voles are described as a model system for which evidence of monogamy exists under both field and laboratory conditions. Using this model we will describe a variety of endocrine factors capable of influencing the expression of specific components of monogamy, including pair bonding, male parental care, alloparenting and reproductive suppression, and we propose mechanisms through which ontogenetic interactions among the adrenal and gonadal axes could regulate the development of the characteristics of monogamy. Concurrently, we will use these observations to suggest several hypotheses regarding the neurochemical control of social behavior. To date research on the behavioral endocrinology of monogamy has focused on the effects of steroids from the gonads and adrenal glands and the neuropeptides, oxytocin and vasopressin.

VOLES AS A MODEL SYSTEM FOR THE ANALYSIS OF THE BIOLOGY OF MONOGAMY

Monogamy has been most clearly demonstrated in mammals that are not readily available for laboratory study. The identification of several monogamous rodents opens the possibility of physiological investigations of mammalian monogamy. At present the best studied of these rodents are prairie voles (*Microtus ochrogaster*). Several closely related species, including both monogamous and nonmonogamous voles, are available for coordinated field and laboratory investigation. Voles are found in diverse habitats. They show dramatic and rapid fluctuations in density, and have long been a favored subject for ecological studies of mammalian population dynamics (39,45,67,92). Voles show remarkable species diversity in social organization and mating systems, which range from monogamous prairie and pine (*Microtus pinetorum*) voles, to more polygynous species, such as meadow (*Microtus pennsylvanicus*) and montane (*Microtus montanus*) voles (33).

Voles have not undergone domestication, and can be studied in nature, yet have many of the attributes of laboratory animals. They breed quickly and readily in the laboratory and provide comparatively inexpensive subjects suitable for most aspects of biological investigation, except those requiring large body size. The abundant accessibility of these rodents, and their wide geographic distribution (92), allows hypotheses that are generated in the laboratory to be tested under natural conditions and vice versa; in this regard voles are somewhat unique among "laboratory" animals.

NATURAL HISTORY, SOCIAL ORGANIZATION, AND MONOGAMY IN PRAIRIE VOLES

The first evidence for monogamy in prairie voles came from field observations (44). Male and female pairs tend to be trapped together over several months. Pairs remain together even at times when the female is not reproductively active. In prairie voles the most common family group in nature consists of one adult male and one adult female and one or more litters of their offspring. Such families here will be termed monogamous. Offspring that do not disperse, but remain within the natal nest, are termed philopatric; the social organization of prairie voles offers a clear example of philopatry and cooperative breeding (16).

Based on field data from prairie habitats in Illinois (45,67) it was found that about 70 percent of juvenile prairie voles do not disperse, but in fact remain with their family to form philopatric communal groups. However, juvenile mortality is high (85-90%) and communal groups typically only occur in late autumn and winter when predation on young is low. Snakes are the major summer predators of young voles; animals that have reached adulthood are less likely to be affected by predation.

During the warmer months in central Illinois, most of the social groups identified are either male-female pairs, single females (known to be survivors of a pair), or small communal groups (with an average size of three individuals). In late autumn and winter larger communal groups become common, and may include 10-12 adults. These communal groups usually consist of an established breeding pair and in some cases there is evidence of breeding by philopatric offspring.

A substantial pool of "wandering" unpaired males exist within natural populations (45% of the adult males). Inbreeding is apparently rare. However, at high population densities, resident males may not be able to exclude all intruders, and philopatric females living within communal groups may become pregnant. (Reproductively active philopatric females most likely mate with nonresident wandering males.) In the spring surviving members of communal groups typically break up into male-female pairs. Only 2% of the newly formed spring breeding pairs involve related animals. Within family groups about three-fourths of the adult pairs remain together until one member dies. In less than 10% of cases there is evidence that the male has abandoned his female partner. After the death of one member of a pair fewer than 20% of the survivors eventually acquire a new mate.

Prairie voles are believed to have evolved in tallgrass prairies, which are very low food resource habitats. Prairie vole population densities in this habitat remain relatively low and females are widely dispersed. The social organization and mating system of prairie voles may have evolved as an adaptation to a low food resource habitat (45,67). According to this hypothesis, under low population densities selective pressure would favor monogamous male-female pairs, and in some cases permit communal groups, which include nonreproductive philopatric offspring as helpers. Under conditions of high food resources (such as those studied most intensively in Illinois), mate guarding and other adaptations of monogamy might be inadequate to maintain a sexually monogamous social system.

Pair Bonding in the Context of Natural History

Pair bonding is a hypothetical construct which we assess through measurements of partner preference, selective social contact and selective intrasexual aggression. Animals must select mating and social partners and defend themselves and their environment (nest, mate, offspring, etc) from intruders of the same or opposite sex.

As described above, monogamous pairs or communal groups arising from monogamous pairs are the most common breeding groups in nature. Additional pregnant females are sometimes found in communal groups (67). It is likely that there is only one sexually active male (the father) in a family group. Inexperienced males are not aggressive and usually cannot supplant experienced breeders (40). Males with sexual experience, but without a partner may form the category of "wandering" males that has been observed by in nature. These males may be too aggressive to live in a group containing another male.

However, males that are not living in groups may have some reproductive success by mating with single females and with young females that have remained within the communal family; the latter is most likely under high resource and high population conditions, when mate-guarding breaks down.

Female prairie voles are selectively aggressive to unfamiliar females (38), and probably use this method to reduce intrusions into the family. Intruding females could offer sexual competition and also might commit infanticide. In the laboratory pup attacks are about twice as common in reproductively naive young females (20%) as in males (11%); adult animals of either sex that have been housed with their family never attack pups (83).

In nature, surviving juveniles may remain with their families throughout their entire lives, resulting in the development, when the environment permits, of communal philopatric groups. The average age of dispersal in prairie voles that do leave the natal group is 45–55 days of age (67). These animals are old enough to breed successfully, but offspring that remain with their families usually do not reproduce. After separation from the family, laboratory results suggest that incest avoidance would probably last 1–2 wk (42). In addition, even when given the opportunity to mate with a nonfamily member, we have found that males that have been living with their families require several days of isolation and/or exposure to novel females to become sexually active. These results suggest that reproduction in philopatric males is suppressed by behavioral processes, rather than reflecting an inability to reproduce.

Reproductively naive voles are uniformly social to other nonaggressive animals. Depending on population density, dispersing females probably select a mate from a pool of animals that may include males that are either sexually naive or in some cases sexually experienced, unpaired males. Dispersing females would probably initially select a novel male and ignore a male sibling. However, if siblings are separated for a period of weeks without successfully finding unrelated partners they might lose the ability to recognize each other and thus eventually could mate. Under conditions of very low population densities, which are common in nature, the capacity of separated siblings to eventually overcome an incest avoidance might be adaptive.

We have examined the basic responses of reproductively naive females to various categories of males (40,42,44) and found that females essentially ignored their male siblings. [Male siblings are ineffective in inducing estrus in their sisters for this reason (15).] These females investigated unfamiliar, sexually inexperienced males and engaged in behaviors that were likely to lead to pairing and reproduction. Initial encounters with sexually experienced males included agonistic behaviors that might have provided a behavioral barrier to reproduction, thus encouraging the new pairs to be composed of reproductively naive animals.

In summary, the behaviors shown by prairie voles in the laboratory are consistent with a monogamous-communal social system. We believe that partner preferences and the aggressive responses of individual voles may be mechanisms underlying the structure of prairie vole family groups.

CHARACTERISTICS OF PAIR BONDING IN VOLES IN THE LABORATORY

Research from several sources (13,14,17,18,32,41,93) has described the social behavior of prairie voles and related species in some detail. The results from this work suggest that the following behaviors are indicative of pair bonding.

Partner Preferences

Prairie voles show a preference for contact with a familiar sexual partner in a choice preference test and/or other differential behavior in dyadic encounters or in preference tests (14,20,41). A simple paradigm has been established for testing partner preferences (107). Physical contact (side by side behavior in both dyadic encounters and preference tests) selectively increases in male-female pairs with a history of cohabitation and/or mating (21,107).

Our test procedure gives animals a choice of a neutral chamber and two tethered stimulus animal chambers. Prairie voles in general are highly social and spend most of their time in the chamber with another animal, although the time in physical contact varies as a function of the social history of the animal. Female prairie voles spent approximately 20% of their time alone in the neutral chamber. In contrast, under comparable test conditions, polygynous montane voles remained alone about 90% of the time.

Anesthetized partners elicited preferences that were similar to those shown toward awake animals when females were allowed to choose between a familiar and unfamiliar partner (107). These results suggest that stimulus qualities of the animal, other than active behavior, are adequate for choices to occur.

Preferences for a familiar partner, formed by 24 h of cohabitation, begin to decline, but are still significant, after approximately 8 days of separation, and are no longer significant when animals have been separated for 10 days (A. C. DeVries, unpublished). Eight to fifteen days of separation results in a loss of incest avoidance among siblings or unrelated animals that have been reared together since infancy (42). Taken together these findings suggest that the functional "social memory" of prairie voles lasts between 1 and 2 wk.

Sexual preferences do not always correlate with social preferences. We initially attempted to use sexual preference as an index of the development of partner preference. Although well-established breeding pairs tended to show a sexual preference for each other (44), in newly formed pairs, females elected to copulate equally with familiar and unfamiliar males (14,17,18). Repeated studies of this phenomenon suggest that voles are more discriminating in their social interactions than in their selection of a sexual partner. Preliminary field data and lab studies, using DNA fingerprints, indicate that females may carry litters of mixed paternity (17) and support the assumption that sexual exclusivity is not an essential characteristic of prairie vole monogamy. In spite of the absence of sexual exclusivity, our research indicates that social preferences, and especially physical contact, are reliable indices of partner preferences (18,107). Sexual preferences are more difficult to study than social preferences because ideally one should balance the hormonal history of both the experimental and stimulus animals; however, because hormonal conditions can be rapidly altered by social and sexual interactions it is difficult to maintain this balance.

Selective Aggression

Intrasexual aggression toward unfamiliar conspecifics may be an expression of mate guarding in monogamous mammals (31). Reproductively naive prairie voles are rarely aggressive. Sexually experienced male prairie voles are highly aggressive toward strangers (43,45). In reproductively naive males aggression increases within approximately 24 h after the onset of mating (112). Males that have experienced nonsexual cohabi-

tation with a female for 24–72 h show slight, but usually not significant, increases in aggression.

In reproductively naive females the development of aggressivity follows a different pattern from the aggression seen in males (38,40). Females with a history of breeding, with or without pups present, show increased aggression toward intruders of both sexes. Sexually experienced females with an established mate will attack unfamiliar males and, even when in heat, in some, but not all, cases may reject the sexual advances of unfamiliar males (44). This behavior presumably helps to maintain the pair bond of established pairs. However, preliminary results from DNA fingerprinting have suggested that litters of mixed paternity are not uncommon.

We have compared aggression following mating in females to that seen in males. Although females without a prior sexual history do show some intrasexual aggression within 24 h following mating, the intensity is much lower than that seen in males; these females may still be under the influence of the hormones that induce estrus (20). By the time pregnant females are ready to deliver they have become highly aggressive and usually will not tolerate cohabitation with an unfamiliar female (38,40, Williams, unpublished data). The time course of the onset of aggression during pregnancy remains to be described.

Nest Site Selection

Prairie voles are selective in nest sites and prefer to build a nest in an area that has contained the partner vs. another animal (76). In nature and in semi-natural settings male voles are primarily responsible for nest construction. We have found that females will, over a period of hours, carry nesting materials to a preferred partner. Under comparable conditions males distributed nesting materials equally to familiar and unfamiliar females (Reeder and Carter, unpublished data). Resource sharing offers a possible index of partner preferences, at least in females.

Adrenal Responses to Separation

Adrenal responses to separation from a partner provide another possible index of pair bonding. Corticosterone responses in both males and females are affected by the presence or absence of a partner. Separation has been shown to influence glucocorticoid responses in monogamous titi monkeys (71).

Corticosterone levels also may vary as a function of separation and reunion in prairie voles (Williams, et al., manuscript in preparation). In one experiment we examined corticosterone levels in ovariectomized females and intact males that were paired for 2 wk [(a) baseline], and then separated for 24 h [(b) separated], or separated for 24 h and then reunited with the familiar partner for 30 min [(c) reunion, partner] or separated and then placed with an unfamiliar reproductively naive partner [(d) unfamiliar]. Females had higher baseline levels of corticosterone and showed more dramatic responses to social stimuli than did males, but the directional responses to social separation and reunion were similar in both sexes. Separation from the partner (b) produced a slight increase in corticosterone, and reunion with the familiar partner (c) was associated with significant declines in corticosterone levels to below baseline. Females that were placed with an unfamiliar partner (d) had levels of corticosterone that were elevated, particularly in comparison to corticosterone levels following reunion with the partner. In a separate experiment we found

that reproductively naive males and females, that had not previously experienced cohabitation with an adult, nonfamily member, responded to their first encounter with a stranger of the opposite sex by showing a rapid decline in corticosterone. An increase in corticosterone is traditionally viewed as a stress response (64). From this perspective prairie voles that have established pair bonds (but not unpaired animals) may find exposure to an stranger stressful, while reunion with a familiar partner may be interpreted as a stress-reducing stimulus. In general these results support the hypothesis that pair bonding is physiologically significant for this species.

Intra- and Interspecific Variations in the Expression of Monogamy

As mentioned above, species differences in social behavior have been observed within the genus *Microtus*. For example, male parental care and care of infants by older juveniles (alloparenting) are prominent features of monogamy and are readily observed among various species of the genus *Microtus* (16,30,33,47,50,77,87,93,100,110). Recent studies within prairie voles, *Microtus ochrogaster*, indicate that animals reared from a stock originally captured in Illinois differ in the expression of alloparenting when compared to prairie voles, presumably of the same subspecies, captured in Kansas (Roberts, et al., manuscript in preparation). Reproductively naive male and females of the Illinois populations showed high levels of pup directed behaviors, while males from the Kansas population spent relatively less time with pups than did Illinois males, and naive females from the Kansas population often ignored or attacked infants. High levels of biparental care were seen in both populations when parents were tested with their own pups, suggesting that priming effects associated with reproductive activities, such as mating or pregnancy, are less necessary in the regulation of parental care in prairie voles that originated in Illinois. Additional evidence in support of within species variation in indices of monogamy is the finding that Kansas prairie voles are anatomically more sexually dimorphic in body weight and anogenital distances than are Illinois prairie voles. In conjunction with field data, these findings suggest that prairie voles from Kansas show fewer indices of monogamy than do those from Illinois. Analyses of the sources of within-species variation may offer insights into the proximate and ultimate mechanisms underlying monogamy. In addition, as in other vertebrates (65) the expression of monogamy in prairie voles may vary as a function of habitat or other ecological and evolutionary constraints.

HORMONES AND PAIR BONDING IN PRAIRIE VOLES

Recent research with prairie voles has implicated several hormones, and in particular oxytocin, vasopressin and corticosterone, in partner preference formation, selective aggression and male parental care. These findings are reviewed below, followed by speculation regarding the possible effects that interactions among these hormones might have in the development of pair bonding in prairie voles. Studies from our laboratory were conducted with prairie voles from a stock captured in Illinois (Table 1).

Gonadal Hormones and Pair Bonding

Partner preferences develop in intact females in male-induced estrus or in ovariectomized females in estradiol benzoate-induced estrus (21,107). Thus postcopulatory changes in ovarian activity, such as those associated with pregnancy, are

TABLE 1
FACTORS INFLUENCING PARTNER PREFERENCE, INTRA-SEXUAL AGGRESSION AND PARENTAL CARE IN PRAIRIE VOLES

Test – Treatment	Male: Partner preference	Male: Same-sex aggression	Male: Pup-care	Female: Partner preference	Female: Same-sex aggression	Female: Pup-care
Cohabitation	preference development facilitated by prolonged cohabitation	low-moderate	high	preference development facilitated after prolonged cohabitation	low	high
Sexual experience	preference development facilitated	high	high	preference development facilitated after brief mating	low*	high
Gonadectomy & cohabitation	no affect on parameters of preference development	low-moderate	reduced	no affect on parameters of preference development	low	NA
Adrenalectomy & cohabitation	preference development inhibited	low-moderate	NA	preference development facilitated after only 1 hr cohabitation	low	NA
Estrogen (2 days)	NA	NA	NA	no affect on preference development	low, but slightly increased	NA
Corticosterone	preference facilitated by cort injection after brief cohabitation	NA	high	inhibits preference development	low	NA
Oxytocin (CNS)	no affect on preference development (low dose OT)**	low	NA	preference development facilitated	low	NA
Vasopressin (CNS)	preference development facilitated	moderate-high (without mating)	very high	NA	NA	NA

NA = No information available at this time.

*Females that are in late pregnancy (44) or postpartum estrus (113) are highly aggressive.

**Doses of OT used in males, were matched to doses of vasopressin that were effective in increasing aggression (112), but were lower than those effective in females (108).

not essential in females to permit postcopulatory increases in partner preferences to form. Exogenous oxytocin facilitates partner preference formation in ovariectomized female prairie voles (108), indicating that ovarian steroids also are not essential for partner preference formation in this paradigm.

The patterns of behavior associated with pair bonding in prairie voles are sexually dimorphic. Reproductively naive male prairie voles show a transient increase in aggression when they are first exposed to a female, but this aggression declines if males do not experience mating. Within 24 h following mating there is a rapid and long-lasting postcopulatory increase in aggression. Females do not become aggressive following cohabitation and show slight increases in aggressivity immediately following mating (Carter, unpublished data), but require days or weeks to become maximally aggressive (38).

The testes and testosterone have been implicated in both the regulation of male parental care and in the production of central vasopressin in prairie voles (27,28,99,100). Low levels of gonadal hormones are generally, but not always, associated with lower levels of aggression in other species (60,61,73). The possible effects of gonadal hormones on selective aggression in prairie voles remains unclear. Aggression is rare in sexually naive male prairie voles. Copulatory stimulation is needed to trigger maximal aggression in males, and since castrated males

rarely mate we have not been able to examine the behavioral effects of copulatory stimulation in the absence of androgens. We have examined the possibility that gonadectomized and/or adrenalectomized males might show increases in aggression following several days of nonsexual cohabitation. Neither castration nor adrenalectomy for one to 2 wk altered the response to cohabitation in male prairie voles; operated and intact animals showed slight increases in aggression following cohabitation that were not affected treatment (Hastings, et al., manuscript in preparation). However, postcopulatory declines in the CNS content of immunoreactive vasopressin require a period of at least 4–6 wk to occur. Thus, our data do not discount the possibility that central peptides, possibly regulated by gonadal hormones, may be involved in selective aggression.

ADRENALECTOMY AND PARTNER PREFERENCES

The effects of adrenalectomy on partner preferences is sexually dimorphic in prairie voles: adrenalectomy inhibits partner preference formation in male prairie voles, and facilitates partner preference formation in female prairie voles (26). Because partner preferences can form quickly in females, the paradigms necessary to describe facilitations in females require short exposures. In adrenally intact females, exposures

of less than 3 h do not produce partner preferences, while in adrenalectomized females as little as 1 h of cohabitation leads to a strong preference for the cohabitating male. Corticosterone injections inhibited partner preference formation in this paradigm in adrenalectomized females. In contrast, adrenalectomized males do not show significant partner preferences even after exposures of as long as 24 h, while adrenally intact males usually form preferences for a cohabitating partner in this time period.

CORTICOSTERONE AND PARTNER PREFERENCES

Acute corticosterone injections facilitate partner preference formation in adrenally intact male, but not female, prairie voles (26). Partner preferences were assessed in intact male prairie voles receiving a single intraperitoneal injection of corticosterone (2, 20, or 200 ug), followed immediately by 6 h of cohabitation with an ovariectomized female, and then a preference test allowing a choice between the familiar partner or a comparable novel female. Treatment with either 20 or 200 ug produced a significant increase in preferences for a female partner with which the corticosterone-treated male had cohabitated. Males receiving a low dose of corticosterone (2 ug) showed a slight preference for the partner, while oil-treated control males showed a preference for the novel female under these test conditions. Comparable corticosterone injections inhibit partner preference development in both intact and adrenalectomized female prairie voles.

The mechanisms responsible for sex differences in the behavioral effects of adrenalectomy and corticosterone in prairie voles remain to be described. In rats there are sex differences in the reactivity of the adrenal axis, and in the stimulation required to induce a stress-related release into the bloodstream of hypothalamic neuropeptides, such as oxytocin. In rats, the stress-induced release of oxytocin is more pronounced in females than in males (22). Postnatal exposure to testosterone produces females that show a male-like oxytocin response pattern, although neonatal castration does not enhance the oxytocin response in male rats (23).

OXYTOCIN AND PARTNER PREFERENCES

Oxytocin is released by genital stimulation in males (75) and females (10,54) in a variety of species. In adult rats non-genital tactile contact releases oxytocin, even in anesthetized animals (91). Oxytocin also has been implicated in sexual behavior (8,11) and maternal behavior (79) in several species. Oxytocin, released during parturition or genital stimulation, facilitates the development of selective mother-infant bonds in sheep (55,56). In addition, oxytocin increases social contact in female prairie voles (115), in rats of both sexes (116) and in male squirrel monkeys (111).

As described above, in prairie voles copulatory interactions hasten partner preference formation (14,17,21,107) and are necessary for the induction of selective aggression (112). Based on these findings we hypothesized that oxytocin might play a role in the coordination of mammalian social experiences, such as mating, with the expression of subsequent social behaviors and the development of partner preferences.

Tests of this hypothesis were conducted by exposing ovariectomized female prairie voles to oxytocin and subsequent nonsexual cohabitation with a male partner. Immediately after cohabitation ovariectomized females were tested for their preference for either the cohabitating partner or an unfamiliar male. Centrally (ICV) infused oxytocin significantly facilitated the formation of selective partner preferences (108).

These effects were dose-dependent (seen at 10 and 100 ng/h, but not at 1 ng/h). Combined infusions of oxytocin in conjunction with a selective antagonist for the oxytocin receptors [oxytocin antagonist (OTA) = d(CH₂)₅[Tyr(Me)², Thr⁴, Tyr-NH₂⁷] (Peninsula Laboratories, Belmont, CA)] no longer produced a significant increase in partner preferences, suggesting that the observed effects of oxytocin may act through the oxytocin receptor. Control substances administered ICV or SC infusions (100 ng/h) of oxytocin did not affect preference behavior. These results indicate that oxytocin treatments can facilitate partner preference formation even in ovariectomized females, without exogenous estrogen. Whether, endogenous oxytocin release is responsible for the behavioral changes following mating or cohabitation remains to be determined.

The behavioral effects of oxytocin in males have not been studied in depth. However, low doses of oxytocin, below those needed to obtain behavioral effects in females, did not facilitate partner preference formation in male prairie voles (112).

OXYTOCIN AND AGGRESSION

Selective aggression is an integral component of pair bonding. In males aggression toward other males increases dramatically following mating (112), suggesting that the physiological events associated with sexual experience can modulate this behavior. As discussed above, oxytocin is released during mating in several species. Male prairie voles given ICV injections of large doses of oxytocin showed an immediate inhibition of sexual behavior. Aggression was low in these tests and not affected by oxytocin (66). In a separate study, male-male aggression did not change following ICV oxytocin infusions, and a selective oxytocin receptor antagonist did not inhibit male-male aggression following sexual experience (112). Thus, oxytocin is probably not involved in the mating-related induction of aggressivity in male prairie voles.

We also have considered the possibility that oxytocin might influence the expression of aggression in female prairie voles (115). Females that were given prior estrogen priming followed by ICV oxytocin injections showed decreased male-directed aggression. Declines in aggression were seen across a broad dose range and occurred following doses that inhibited lordosis (1000 ng), after ICV doses that partially inhibited lordosis (300 ng), and even when given in a very low dose that did not affect female sexual behavior (1 ng). In general these results suggest that oxytocin is associated with reduced aggression, and is not likely to be responsible for the augmentation of aggression that follows mating in either sex.

VASOPRESSIN AND PARTNER PREFERENCES

In males, vasopressin infusion increased partner preferences for the female present during the infusion and a vasopressin-antagonist blocked this preference (112). Vasopressin synthesis is androgen dependent in several brain regions (28,98). This androgen dependence may coordinate the behavioral actions of vasopressin with the endocrine status of the male, and may account for certain aspects of sex differences in behavior.

In a preliminary study of female prairie voles, a selective antagonist for vasopressin V1a receptors [(d(CH₂)₅)[TYR(Me)]-AVP, Peninsula Laboratories, here termed AVPA] blocked the development of a partner preference, which typically follows cohabitation. We have not yet examined the behavioral effects of vasopressin agonists in females.

VASOPRESSIN AND AGGRESSION

Based on studies that have implicated vasopressin in territorial aggression in hamsters (37) and the finding that vasopressin release is associated with sexual behavior (5,75), we hypothesized that vasopressin might play a role in the observed postcopulatory increase in aggression. The vasopressin receptor antagonist, AVPA, was administered at the onset of mating. AVPA, in doses between 50 pg–500 ng, did not block sexual behavior, but did prevent the associated postcopulatory increase in male-male aggression (112). These doses are low when compared to data on other behavioral effects of the AVPA compound, and suggest that the antagonist is working through a physiological mechanism. Furthermore, when AVPA was given following mating, it no longer interfered with aggression, indicating that it is the development of aggression, rather than its expression, that is blocked. Central injections (ICV) of vasopressin, in the absence of mating, significantly increased selective aggression in male voles. These results offer evidence for a role for vasopressin in the development of male-male aggression in prairie voles. Selective aggression toward intruders is probably a form of mate guarding, and may be functionally equivalent to territorial defense.

MALE AND JUVENILE PARENTAL CARE

Care of infants by either males or nonreproductive juveniles is a feature of prairie vole monogamy (16,47,50,77,93,100,101,110). Recent data implicates both androgens and vasopressin in male parental care in this species. Castration in adulthood reduced pup-directed behaviors in sexually naive male prairie voles. Castration also reduced the number of AVP-immunoreactive (AVP-ir) cells in the bed nucleus of the stria terminalis (BST) and medial amygdaloid nucleus (MA), as well as the density of AVP-ir fibers in the lateral septum (LS), which receives input from the BST and MA. Implantation of testosterone at the time of castration restored normal parental care and vasopressin levels (98). When vasopressin was implanted in the LS, but not in other areas, males showed more pup-directed contact and increased the time spent crouching over the pups. Treatment with antagonists for type V1a vasopressin receptors inhibited the effects of exogenous vasopressin and was associated with reduced pup care in normal males (99). Wang and associates (98,99) hypothesize that vasopressin might be released normally by events associated with the exposure to pups, including the ingestion of salty urine from the pups.

The possible role of peptide hormones, such as vasopressin, in juvenile care giving or alloparenting has not been studied. Such hormones might facilitate alloparenting through mechanisms related to those described for male parental care (99). As discussed above, both mating and androgens may facilitate male parental care. However, juvenile males and females engage in alloparenting without the benefit of either sexual experience or adult levels of gonadal hormones. Thus, mechanisms responsible for alloparenting may differ from those responsible for either male or female parental care.

Prolactin is another reproductive hormone which plays a role in maternal behavior (7) and which has been implicated in male parental care in monogamous mammals including common marmosets (34) and California mice (*Peromyscus californicus*) (48). In California mice nonparental males may be infanticidal and the expression of male parental care requires chemosignals from a female, which can in turn release prolactin. In prairie voles, males rarely attack pups and are usually

spontaneously paternal, even in the absence of cues from a female. The role of prolactin in prairie vole parental behavior has not to our knowledge been studied. However, we hypothesize based on the differential roles of social stimuli in prairie voles, vs. California mice, that either male prairie voles release prolactin in the absence of female stimulation, or do not require neuroendocrine priming by prolactin for the expression of male parental care. The expression of alloparenting and male parental care in prairie voles may depend on physiological mechanisms that differ from those responsible for either maternal behavior or male parental care in less philopatric species, such as California mice (16).

OTHER NEUROCHEMICALS AND SOCIAL BONDING

Various neurochemicals have been implicated in social, sexual and maternal behavior in nonmonogamous mammals. Among these, prolactin (7), endogenous opiates, (78), and catecholamines (54) have been associated with parental behavior and social attachment. These chemicals also regulate oxytocin release (62,63,97). It is plausible that these and other neurochemicals are part of the endogenous control of pair bonding, although research on the behavioral effects of these chemicals in voles is not yet available.

Most of the existing research on behaviors associated with monogamy, and in particular pair bonding, has described these behaviors in the context of reproduction, and has focused on reproductive hormones. However, we also may gain insights into the physiology of social behavior, by considering the possibility that social behaviors are of such importance to monogamous mammals, that these behaviors share the properties of a fundamental reward system. Thus, the formation of a pair bond, or separation of paired animals might trigger physiological responses that parallel those found in the development of drug addiction or the expression of withdrawal symptoms. For example, the neuropeptides that have been implicated in monogamous behaviors have also been implicated in substance abuse. In rats, oxytocin inhibits the development of tolerance and other responses to opiates and cocaine. Oxytocin treatment reduces dopamine utilization and the number of apparent binding sites for dopamine. Based on these findings Sarnyai and Kovacs (85) have proposed that oxytocin acts as a neuromodulator of dopaminergic activity, which in turn regulates CNS processes leading to drug addiction. Similar processes might influence the characteristics of monogamy.

NEURAL CORRELATES OF PAIR BONDING AND MONOGAMY

Species Differences in Peptide Receptors

Oxytocin and vasopressin receptor distributions, measured by receptor autoradiography, differ between monogamous and polygamous voles of the genus *Microtus* (51). These species do not differ in the distribution of receptors for the mu opioids or benzodiazepines. The functional significance of patterns of distributions of oxytocin or vasopressin receptors remains to be described. However, receptor availability in specific brain areas may be related to species specificity in the expression of social and sexual behaviors among monogamous and nonmonogamous mammalian species.

Hormonal Effects on Oxytocin Receptors

Oxytocin receptors are generally steroid dependent in rats, and there are reports that both estrogen and progesterone regulate oxytocin receptor distributions in the hypothalamus

(89). Because of these findings we also examined oxytocin receptor binding as a function of hormonal status and sexual experience in female prairie voles (114). The results of this study confirmed the presence of oxytocin receptors in a number of areas of the limbic system that have been implicated in sexual behavior, social behavior and aggression, although the pattern of oxytocin receptors differed from that seen in rats. In spite of large samples ($N = 10$ in most groups), quantitative densitometry in female prairie voles revealed steroid dependent increases in oxytocin receptors only in the anterior olfactory nucleus. In marked contrast to rats, hypothalamic oxytocin receptors were not hormone dependent.

Oxytocin receptors in the hypothalamus are presumed to play a role in the facilitation of sexual behavior in rats (8,9,89). In contrast, hypothalamic oxytocin receptors are apparently less influenced by gonadal steroids in prairie voles, and manipulations of oxytocin do not facilitate female sexual behavior in this species. Species differences in the peptidergic regulation of hypothalamic nuclei may be related to species differences in the hormones needed for the activation of sexual behavior. For example, ovariectomized female prairie voles require only estrogen for estrus induction (19,35), while estrogen-priming followed by progesterone is maximally effective in nonmonogamous hamsters and rats (12).

The behavioral effect of oxytocin in rats is also facilitated by priming with either progesterone (117) or adrenal hormones, including corticosterone (8). The behavioral effect of oxytocin in prairie voles also may be modulated by adrenal hormones. Prairie voles secrete corticosterone at levels that are about ten times higher than those produced in rats (Taymans, et al., manuscript in preparation). The exceptionally high levels of adrenal hormones in prairie voles might functionally substitute for the behavioral effects of progesterone. Adrenal hormones also might affect the expression of oxytocin receptors, thus masking possible effects of progesterone in this species.

Prairie voles do not have an estrous cycle, and, even in comparison to other rodents (95), are highly dependent on olfactory cues for natural estrus induction (15,36,59). There is evidence that olfactory cues are used in partner identification in prairie voles. Bilateral olfactory bulbectomy reduced estrus induction, partner preferences and overall social contact. However, unilateral bulbectomy did not influence social contact or estrus induction, but did eliminate partner preferences (109). Prairie voles also depend heavily on olfaction for partner recognition (59,76,107). Modulation of sensory processing has been implicated in the behavioral effects of peptides in amphibia (74). Olfactory processing or partner recognition might be regulated by an interaction between oxytocin and estrogen in prairie voles. These results suggest the testable hypothesis that neural changes associated with unilateral bulbectomy, rather than olfaction per se, may play a role in the development and/or expression of partner preferences in this species.

Hormonal Effects on Vasopressin

Testosterone regulates vasopressin immunoreactivity in male prairie voles (98). In male prairie voles castration is followed by reductions in vasopressin in immunoreactive cell bodies originating in the medial amygdala and bed nucleus of the stria and terminating in the lateral septal nucleus, and testosterone replacement therapy restores vasopressin to the precastration pattern. Vasopressin immunoreactivity in these areas also differs between sexually naive vs. sexually experi-

enced male prairie (but not montane) voles (4). The lateral septum is a site of action for vasopressin in the regulation of male parental care (99), but the role of the lateral septum in pair bonding has not yet been examined.

VASOPRESSIN AND THE DEFENSE OF HOMEOSTASIS

In vertebrates, vasopressin is associated with water retention (anti-diuresis), regulation of the cardiovascular and autonomic nervous system, and also is a central component of the adrenal stress axis. The well-documented capacity of vasopressin to regulate flank marking and other forms of territorial and agonistic behavior in hamsters (2,37), may represent a form of territorial defense. (Hamsters are exceptionally solitary animals that are adapted to a xeric habitat. Water and resource conservation are vital for this species, and the behavioral effects of vasopressin might be especially apparent in solitary and/or resource-limited species.) In addition, CSF vasopressin levels are elevated in patients with obsessive-compulsive disorder (3). The cognitive content of human obsessions often includes themes of a self-defensive nature (Altemus, personal communication). Vasopressin release increases during or after sexual behavior in male humans (75) and male prairie vole (4,5). Collectively these observations suggested the hypothesis that vasopressin also might play a role in the increased aggressivity and "mate defense or guarding" that arises following mating in male prairie voles (43,44). As described above, tests of this hypothesis have revealed that vasopressin antagonists reduce postcopulatory aggression and centrally administered vasopressin increases aggression (112).

VASOPRESSIN, OXYTOCIN AND THE EVOLUTION OF SOCIAL BEHAVIOR

Vasopressin-like peptides have been identified in mollusks and van Kesteren and associates (96) suggest that "prohormones of the vasopressin/oxytocin superfamily must have been present in the common ancestors of vertebrates and invertebrates." Even snails respond to vasopressin with "defensive behavioral reactions" (58). Thus, vasopressin-like molecules are ancient, found in both vertebrates and invertebrates, and associated with "adaptive" behaviors (74,96).

Oxytocin is an integral part of the neuroendocrine system that regulates birth and lactation, which in turn define Mammalia. A growing literature on oxytocin implicates this molecule in maternal, sexual and social behavior (19,79). The literature revealing many neurobiological interactions between oxytocin and vasopressin (described in various chapters in 77), and our findings that simple social contact, as well as partner preferences, can be enhanced by oxytocin (115), suggest the hypothesis that oxytocin may have evolved as a natural "anti-vasopressin."

For mammalian reproduction to succeed, self-defense and asociality must be subjugated to sociality, at least during birth, lactation, sexual behavior and as needed to allow social organization. Perhaps the important task of regulating the interaction between social and agonistic behaviors is managed, in part, by an interaction between two related neurochemical systems that incorporate oxytocin and vasopressin in their functions. Although the work described here and much of the available research focus on mammalian hormones, birds and other vertebrates could have accomplished a similar task using other variants of these peptides, such as mesotocin and vasotocin (74). In addition, Panksepp (76) has shown that vasopressin increases distress calling in chicks, while oxytocin has

particularly powerful behavioral effects in the suppression of separation distress. (This finding is especially intriguing since birds are not known to produce the actual oxytocin molecule.)

A model for studying "social recognition" in male rats has been developed by Dantzer and associates (25). In that model vasopressin is associated with a facilitation of, and oxytocin with an attenuation of, olfactory investigation by adult males toward juvenile stimulus animals. In one-trial passive avoidance tests vasopressin is generally associated with improved avoidance, while oxytocin inhibits avoidance (29). However, in both of these models (as well as in our work described here) emerging evidence suggests that the interactions between oxytocin and vasopressin may be complex (79). De Wied and associates have postulated that there is a "separate neurohypophyseal hormone receptor complex in the brain" that differs from the traditional peripheral vasopressin and oxytocin receptors. Additional work is needed to examine this model in rats, and to determine whether this "hypothetical" receptor system could influence the social behavior of voles.

SEX DIFFERENCES AND THE DEVELOPMENT OF MONOGAMY

Processes Underlying Sexual Dimorphism

Sexual dimorphisms in structure and function are common among polygynous species, but less common among monogamous species. Sex differences in body mass that favor the male are associated with increased sexual competition in polygynous species (30,33). In contrast, in monogamous voles, including prairie voles, males and females are similar in size and weight and general appearance. Anogenital distances are so similar that training is necessary to accurately determine the sex of young prairie voles prior to the descent of the testes, and even trained observers sometimes find it difficult to tell the sexes apart. Shapiro and associates (88) have described in voles a nucleus similar to the "sexually dimorphic nucleus" (SDN) within the preoptic area in rats (46). However, the nucleus was sexually dimorphic only in nonmonogamous voles (montane and meadow voles) and not in monogamous species (prairie voles and pine voles). An additional correlation between neuroanatomy and social organization has been identified by Jacobs and associates (52), who found that the thickness of the hippocampus was larger in males than females among nonmonogamous, but not monogamous, voles. The hippocampus has been associated with spatial memory. Jacobs and associates (52) suggest that species-typical patterns of sexual dimorphism in the hippocampus are related to the fact that nonmonogamous male voles must range further in search of mates than monogamous males, that need only one partner. Thus, on a number of anatomical and functional dimensions monogamous voles appear demasculinized, at least in comparison to polygynous voles.

Based on research with a variety of polygynous mammals, it has been shown that perinatal exposure to hormones, and especially testicular secretions, are necessary for the masculinization of sex differences (46). Sex differences arise from the developmental effects of testicular secretions on the growth and differentiation of sexually dimorphic tissues, including the genitalia and nervous system. In most species perinatal sexual differentiation is followed by a juvenile period of relative quiescence in the reproductive axis, and then by activation effects of hormones during and following puberty. Androgens, possibly after conversion to estrogen, modify the development of various tissues.

Perinatal Stress and Reduced Sexual Dimorphism

Stress experienced by the mother during the last few days of gestation (102–104) or perinatal exposure to adrenal corticoids (including synthetic cortisone) (24) can reduce masculine sexual behavior and the anogenital distance in rats. In rats, perinatal stress also increases male parental care in adulthood (56). Sexual differentiation, and in particular masculinization, as well as adult sexual behavior may be generally suppressed following perinatal stress. Reductions in testicular activity, presumably via elevated activity in the adrenal axis, may follow perinatal stress (103,104). Among the possible mechanisms through which stress could disrupt masculinization is the release of endogenous opiates (53).

In rats the perinatal period (from the late prenatal period through about postnatal day 14) has been termed the "stress hypo-responsive period" (SHRP) and is associated with relative insensitivity of the glucocorticoid release mechanisms (reviewed 69). The SHRP overlaps the period of sexual differentiation. The fact that in rats the adrenal axis is refractory during this period may permit rats to experience a well-defined (at least in comparison to prairie voles) sexual differentiation. The observation that perinatal stress can diminish masculinization in rats, further indicates that even in rats the adrenal axis is not totally insensitive to environmental perturbation during the perinatal period.

Parallels Between the Effects of Perinatal Stress and the Development of Monogamy

Reduced sexual dimorphism and increased male parental care are characteristics of monogamy and also sequelae of exposure to perinatal stress. We hypothesize that adrenal axis activity during the perinatal period might modulate the development of the reproductive system in a manner consistent with the expression of monogamous characteristics. Specifically, we hypothesize that high levels of adrenal activity, which have been measured following brief separation from the mother during the perinatal period in prairie voles (87), may change the nervous system in a manner that reduces sexual dimorphism, promotes male parental care, increases sociality and increases vulnerability to reproductive suppression.

Comparative data offer some support for this hypothesis. Montane voles which are not monogamous have relatively low levels of adrenal activity during postnatal development (87). The characteristics of prairie voles, in contrast to nonmonogamous mammals, may reflect a relative absence of gonadal stimulation during perinatal development. This could occur if the male gonadal axis was inhibited, possibly by hormones of the adrenal axis, during the period of sexual differentiation.

Experiments are in progress examining the effects of perinatal manipulations on prairie vole reproductive development (16,84, Roberts, et al., manuscript in preparation). Preliminary results indicate that male parental care in adulthood, which is normally very pronounced in this species, is inhibited by exposure to exogenous androgen (through daily injections of testosterone) during the first 6 days of life. Males that were castrated on the first day of life showed normal levels of alloparenting. In female prairie voles androgen injections did not increase or decrease pup-directed behaviors. In addition, in females, but not in males, social preferences for strangers vs. family members increased in animals that were exposed to postnatal testosterone, while animals that had received prenatal treatment with corticosterone were more likely to prefer a sibling over a stranger. Thus, exposure to postnatal testosterone may inhibit both paternal behavior in males and social

preferences for a family members, vs. a stranger, in females; conversely, exposure to hormones that are typically associated with stress, such as corticosterone, is associated with increases in male parental behavior and increased preferences for a family member. These observations offer preliminary support for the hypothesis that neonatal exposure to androgens may interfere with social behaviors associated with monogamy, while increased exposure to hormones of the adrenal axis during development may facilitate monogamous behaviors. In conjunction with results from other studies of behavior and brain function, these findings also support the suggestion that males and females may rely on different neurochemical processes for pair bond formation and parental behavior.

SUMMARY

In summary, prairie voles offer an excellent model for the analysis of factors regulating the patterns of social behavior associated with monogamy within the context of natural history. Monogamy in mammals can be influenced by a variety of hormonal processes and apparently involves neuroendocrine substrates that also affect social and sexual behavior in nonmonogamous mammals. The studies described here suggest new hypotheses regarding the functions of the neuropeptides, oxytocin and vasopressin, and implicate the hormones

of the adrenal axis in social behavior. Recent findings indicate that both the organization and activation of behaviors, such as pair bonding and biparental care, which characterize monogamy in prairie voles are regulated by sexually dimorphic processes.

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